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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/389,545	09/03/1999	COLIN R. DUNSTAN	A-605	5554

21069 7590 02/12/2003

AMGEN INCORPORATED
MAIL STOP 27-4-A
ONE AMGEN CENTER DRIVE
THOUSAND OAKS, CA 91320-1799

EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	19

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/389,545	DUNSTAN, COLIN R.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

1. The request filed on 12/5/02 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/389545 is acceptable and a RCE has been established. Claims 41-58 are pending and are currently under prosecution. An action on the RCE follows.

2. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action

3. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

4. The rejection claims under 35 USC 112 second paragraph is withdrawn.

5. The rejection of newly added claims 41-58 under 35 USC 103(a) as being unpatentable over Boyle et al (WO/9723614) and further in view of Conte et al (Annals of Oncology 5:S41-S44, 1994) or Simonet et al (Cell 89, 309-319, 1997) in view of Conte et al is withdrawn in view of the NEW GROUNDS of rejection.

Response to Arguments

6. The rejection of newly added claims 41-46, 48-49, 53-58 under 35 U.S.C. 112, first paragraph is maintained and made again.

The response filed 12/5/02 has been carefully considured but is deemed not to be persuasive. The response states that the rejections be withdrawn for the reasons

made of record. It is assumed that this response is directed to the response filed 5/6/02. In that response the response states that the examples of unfused OPG peptides enable the full scope of the claims and that the examiner has now decided that the examples of unfused OPG polypeptides do not enable any OPG polypeptides or truncated OPG polypeptides (see page 4 of response of 5/6/02). In response to this argument, the argument was directed to Table 1 of WO 97/23614 and as stated in the Office Action mailed 11/6/01, the specification is enabled for OPG polypeptides that are unfused and consist of residues 22-401 of unfused human OPG and only unfused OPG of residues 22-194, 22-200, 22-201, 22-293, and 22-355 of mouse. Table 1 of WO 97/23614 teaches only these constructs result in bioactivity. In addition the art of Simonet et al (Cell 89:309-319, 1997 teaches that loss of the C-terminal portion up to amino acid 194 did not affect activity (see page 315). Therefore the prior art teaches only specific OPG molecules are active and the claims still encompass any OPG of any residues as well as any truncated polypeptides of OPG. In addition, newly added claim 48-49 encompasses OPG fused to any polypeptide and the specification only enables a FcΔC-OPG(22-194) fusion protein for treating bone loss.

The response filed 5/6/02 states that one skilled in the art would readily conclude that patients can be diagnosed as being susceptible to lytic bone disease and would be candidates for treatment with OPG (see page 5 of response). In response to this argument, while this may be true for treatment, prevention of loss of bone mass or abnormal bone formation in not enabled.

The following are some NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

7. Claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 is indefinite for reciting "mature OPG polypeptide" because the phrase is not clear. It is not clear how the "mature OPG polypeptide" is different from that of SEQ ID NO:2 or is there a difference?

Claim Rejections - 35 USC § 103

8. Claims 41-58 are rejected under 35 USC 103(a) as being unpatentable over Boyle et al (WO/9723614) and further in view of Conte et al (Annals of Oncology 5:S41-S44, 1994) and Simonet et al (Cell 89, 309-319, 1997).

The claims are summarized as a method of preventing or treating loss of bone mass associated with cancer comprising administering a polypeptide of SEQ ID NO:2 or a truncated polypeptide or a OPG fusion polypeptide and chemotherapy wherein the cancer has metastasized to bone, wherein the cancer is breast cancer.

Boyle et al teach inhibition of bone resorption and osteoclasts using an effective amount of OPG or a fusion of a fragment of OPG and Fc region of an immunoglobulin (page 36-37, Table 1). Boyle et al also teach the use of the polypeptide for treatment of osteolytic metastasis (see page 37). Boyle et al does not teach treatment of loss of

bone mass using OPG or an Fc fusion protein with OPG or combination therapy with chemotherapy. These deficiencies are made up for in the teachings of Conte et al and Simonet et al.

Conte et al teach treatment of breast cancer lytic metastasis with pamidronate and chemotherapy to delay the progression of bone disease in breast cancer patients and treatment with FC-fusion proteins at 10 mg/kg (see page 318).

Simonet et al teach a method of treatment of ovariectomy-induced bone loss by administration of OPG-Fc fusion protein or OPG. Simonet et al also teach that that OPG can be used for treatment of osteolytic metastases (see page 317) and pamidronate and OPG increased bone density in the femur (see page 315, left and right column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of treatment of loss of bone mass associated with cancer by administration of an OPG polypeptide or an OPG-Fc fusion protein and a chemotherapeutic agent in view of Boyle et al, Conte et al, and Simonet et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of treatment of loss of bone mass associated with cancer by administration of an OPG polypeptide or an OPG-Fc fusion protein and a chemotherapeutic agent in view of Boyle et al, Conte et al, and Simonet et al because Boyle et al teach reduction of osteoclasts with administration of the polypeptides and fusion proteins (see page 128 and Table 1). In addition, one of

ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of treatment of loss of bone mass associated with cancer by administration of an OPG polypeptide or an OPG-Fc fusion protein and a chemotherapeutic agent in view of Boyle et al, Conte et al, and Simonet et al because Conte et al teach a method of treating breast cancer patients with pamidronate and chemotherapy to delay the progression of bone disease in the cancer patient (see page S41). Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of treatment of loss of bone mass associated with cancer by administration of an OPG polypeptide or an OPG-Fc fusion protein and a chemotherapeutic agent in view of Boyle et al, Conte et al, and Simonet et al because Simonet et al teach both compounds of pamidronate and OPG resulted in increased bone density and OPG can be used for osteolytic metastases (see page 315 and 317). Thus, it would have been obvious to use an OPG polypeptide or OPG-Fc fusion protein of Boyle et al and Simonet et al in the method of Conte et al for treatment of loss of bone mass associated with cancer. It would have been obvious to use any chemotherapeutic agent in view of the specification that discloses chemotherapy with drugs known to the skilled worker 9page 32, lines 16-19).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 12/5/02 has been carefully considured but is deemed not to be persuasive. The response states that applicants request that the rejection be withdrawn for the reasons of record. It is assumed that this response is directed to the

response filed 5/6/02. In that response (5/6/02) the response states Pamidronate is a class of compounds which are distinct from OPG and there is no suggestion that one could or should use a completely different anti-resorptive bone agent in combination with a cancer therapy agent and indeed Conte et al states that future research will focus on compounds in the same class (see pages 5-6 of response). In response to these arguments, Simonet et al teach that pamidronate or OPG polypeptides result in increased bone density (see page 315). Thus, it would have been obvious to use OPG or OPG-FC fusion proteins in the method of Conte et la because both pamidronate and OPG result in increased bone density. As stated previously, one would have been motivated by the obvious advantage of inhibition of bone loss with inhibition of the cancer metastasis as taught by Conte et al. In addition, because the claims recite open language the claims encompass a method that uses OPG, pamidronate and chemotherapy in combination.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 42-53, 56-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 42 has been added and recites the limitation of "a method for preventing abnormal bone formation associated with cancer". (This limitation was added in the response filed 9/14/02 as claim 24). The response filed 9/14/01 did not state where support for this limitation can be found. The response filed 5/6/02 states that "as indicated in the specification at page 2, lines 2-9, formation of abnormal bone is accompanied by an increase in osteoclast bone destruction during bone metastases' (see page 5 of response of 5/6/02). The response has been carefully considured but is deemed not to be persuasive. Page 2 of the specification does not disclose preventing abnormal bone formation with the addition of an OPG polypeptide or FC-OPG fusion protein. Applicant is required to provide specific support for the limitation in the specification as originally filed or remove it from the claim.

Conclusion

11. No claim is allowed

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,
Larry R. Helms Ph.D.
703-306-5879